

Chapter 2

Medical Conditions Associated with Nocturia

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Keywords Nocturia • Age • Gender • Ethnicity • Polyuria • Lower urinary tract • Sleep • Socioeconomic • Reproductive • Lifestyle

Background

Nocturia had traditionally been considered part of an array of symptoms of some other primary disorder [1]. In 2002, the standardization subcommittee of the International Continence Society (ICS) proposed the first standardization of nocturia terminology and this report has marked a new era in the approach to the management of nocturia. Since then, nocturia has begun to be recognized as a clinical entity in its own right rather than a symptom of some other disorder, or classed as one of many lower urinary tract symptoms (LUTS) [2]. Although this proposal based on reasonable theoretical considerations has not been tested in any research and should not be taken as the result of scientific enquiry [3], approximately 100 research studies have cited the report within 8 years after its publication. Thus, the report plays a fundamental role of conceptual framework for research on nocturia to understand the possible causative or contributing factors to the pathophysiology of this entity, as the current knowledge on nocturia needs improving in order to advance clinical care.

There are good epidemiological data from worldwide, showing nocturia is a common condition that affects both men and women to an equal extent [4]. The bother experienced by patients with nocturia as well as the impact on quality of life, daytime functioning, and overall health can be severe. Therefore, it is important for the causes of nocturia to be diagnosed accurately so that effective treatment can be

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given as necessary [1]. However, the current knowledge on factors associated with nocturia is limited. Studies of the pathophysiology of nocturia have generally been small and highly focused on one aspect of potential underlying causes [5].

Nocturia is a complex and highly multifactorial condition. According to the ICS report, nocturia can be related to one or a combination of three primary underlying causes, all of which increase with age: bladder storage problems, usually as a component of overactive bladder syndrome (OAB), detrusor overactivity (DO), urgency urinary incontinence, or bladder outlet obstruction (BOO) in men; 24-h polyuria; nocturnal polyuria (NP) as a frequent but often overlooked cause [2]. However, nocturia may be associated with many possible risk factors and comorbidities, such as snoring, obesity, prostate cancer, or restless legs syndrome [4]. These associations may not preclude specific causation, and most are certainly at least potentially contributory to the symptom. While an association between these risk factors and nocturia has been established, estimates of the proportion of patients with nocturia who are in fact affected by each underlying factor are less common in the literature [1]. Factors underlying nocturia may differ between individual patients, but may also coexist within one patient. It is therefore crucial that clinicians and other healthcare providers are well informed as to the characteristic “fingerprints” of each etiological factor, so that they can make treatment decisions which maximize the potential to achieve benefits for the patient [6].

The multifactorial nature of this condition is best demonstrated by the recent findings of the FINNO study which systematically assessed factors related to nocturia in a large population based survey [4]. The factors with the greatest impact for the population were urgency of urination, benign prostatic hyperplasia (BPH), and sleep disruption as manifested by snoring in men. In women, urgency, obesity, and snoring were predictive. Other associations included history of prostate cancer and antidepressant use in men, and coronary artery disease and diabetes in women. In another, multi-institutional study, 60% of subjects had daytime lower urinary tract symptoms (LUTS); one third had cardiac disease and 7% peripheral edema. NP was the most important contributor to nocturia [7]. Finally, it may be necessary to setup multidisciplinary teams to assess patients with nocturia to include urologists, gynecologists, cardiologists, endocrinologists, nephrologists, geriatricians, sleep specialists, as well as allied healthcare professionals such as physiotherapists and nurses [3].

This chapter specifically focuses on what is known about the predictive and risk factors for nocturia. In this chapter, risk factor is used as an aspect of personal behavior or lifestyle, environmental exposure, or inborn or inherited characteristic, which, on the basis of epidemiologic evidence, is known to be associated with nocturia considered important to prevent, while predictive factor means a condition or finding that can be used to help predict whether a patient with nocturia will respond to a specific treatment. Predictive factor may also describe something that increases a person’s risk of developing nocturia. From the point of view of public health, it is important to identify the risk factors for nocturia that might impair the quality of life of the sufferers. This will allow for the provision of lifestyle behavior modification in patients at risk or for treatment of the underlying risk factors, which will be helpful in preventing and treating nocturia [8].

Demographic Factors (Age, Gender, and Ethnicity)

The ICS has defined nocturia as the number of voids recorded during a night's sleep: each void is preceded and followed by sleep [2]. Thus, the term nocturia, in contrast to the definition commonly used before 2002 (≥ 2 nocturnal voids) is not restricted to any particular number of nocturnal voids [9]. Moreover, this definition has excluded predefined thresholds and terms like “bother” and “complaint” because their use could result in a distortion of the determination of incidence, prevalence, course, and risk factors and therefore, this new term is considered a good definition for use in epidemiology studies [10].

Although a substantive association between age and nocturia has been established in several epidemiological studies, nocturia is an underreported condition and, therefore, the true extent of the problem in the population may be underestimated [1]. Adult patients are more likely to consult a provider if they have three or more episodes [11]. Nocturics may be embarrassed or reluctant to discuss their problems [1]. Moreover, they perceive nocturia to be a natural part of aging and therefore may fail to seek medical assistance or may not realize that treatment is available [12].

Several reports of nocturia prevalence exist in the literature. Although Irwin et al. have reported half of all adults to experience nocturia [13], the prevalence rates for nocturia vary considerably, and are affected by the population studied, the definition of nocturia used as stated earlier and the age range considered. For example, some studies investigated nocturia in a population exclusively at specific age groups. This may cause overall rates to be misleading [1]. For instance, Zhang et al. report a prevalence of only 9% in their random sample of Chinese women 20 years old or older. However, 84% of their sample was in fact younger than 50 years and, therefore, the relatively low overall prevalence may be influenced by the predominance of younger participants [14]. Despite these variations in the prevalence of nocturia, there are some findings which are reported repeatedly across studies and countries, when factors such as definitions of nocturia and age of the sample population are consistent [1]. On the other hand, Asplund and Aberg conducted one of the best studies showing prevalence variation due to the definition used for nocturia. They demonstrated a large difference between the incidence of one nocturnal voiding episode ($\cong 50\%$) and two ($\cong 10\%$) or three ($\cong 5\%$) episodes in a questionnaire survey of 3,669 randomly selected women aged 40–64 years in Sweden to assess nocturnal micturition patterns [15].

Bosch and Weiss have recently reported their literature review of 45 studies published in between 1990 and 2009 relating to the prevalence of nocturia in a population sample. They found that 20–44% of women in their 20s and 30s reported experiencing at least one void per night while 4–18% of women in this age category reported two or more voids nightly. Of women in their 70s and 80s, 74–77% reported one or more voids per night while 28–62% reported two or more voids nightly. Of men in their 20s and 30s, 11–35% reported at least one void per night while 2–17% reported two or more voids nightly. Of men in their 70s and 80s, 69–93% reported at least one void per night while 29–59% reported at least two voids per night.

Based on their findings, they concluded that all studies showed a tendency for nocturia to increase with age for both genders [1]. Also, typical ranges for ≥ 2 nocturia episodes/night has been reported as 5–15% for those aged 20–50 years, 20–30% for those aged 50–70 years, and 10–50% for those aged ≥ 70 years [10].

On the other hand, severity of nocturia increases with advanced age, even though more severe nocturia is less common than less severe nocturia. The majority of older men and women experience at least one void per night and on average up to two-thirds experience two or more voids per night. Around half of the population experiences at least one void per night from the age of 50 to 60 years while approximately 25% of the population experiences two or more voids nightly by their early 60s [1].

Descriptive epidemiological data indicate that the prevalence of nocturia increases with age, regardless of the definition used and the steepest increase is in older groups (>65 years) [10]. There are several studies reporting prevalence rates of two or more voids approaching or exceeding 50% in older populations [16] and being as high as 90% for one episode per night in persons over age 80. This increasing prevalence highlights the pervasive nature of this underreported condition [1]. In older age groups, nocturia has been variably associated with chronic medical conditions such as hypertension and diabetes, advancing renal failure, and cardiovascular disease. Nocturia in the frail elderly can cause accidental falls. Frail elderly persons with nocturia, who also have gait and balance disorders and other risk factors for falls, are clearly at increased risk for injury and consequent morbidity. Also, nocturia makes adult patients “feel old” and worry about falling at night [5].

It is well established that nocturia is associated with aging. In general, the incidence and severity of nocturia increases consistently from early adolescence to senescence [10]. However, it is not solely a feature of aging [17]. This increasing prevalence is largely due to age-related physiological changes [18] or pathological conditions that underlie the pathophysiology of nocturia, such as low bladder capacity, NP, or sleep disorders [5]. It is evident that an increase in nighttime urine excretion, causing individuals to rise and void, is part of the normal aging process. Interplay between physiological changes in renal conserving ability and hormonal systems regulating water and sodium handling alters the diurnal rhythm of nocturnal diuresis. These physiological and pathological changes associated with aging explain why NP is believed to contribute to at least 50–65% of cases of nocturia [12]. Finally, with advancing age more time is spent in bed and there are more nighttime awakenings to void. Nocturia can be considered as both a disease and as part of normal association of plasma arginine vasopressin and aging; it is the relative contribution of each of these factors that remains to be clarified [19].

A substantial proportion of younger adults are also affected. In practical terms up to one in five or six younger people consistently wake to void at least twice each night on average. The negative impact of sleep fragmentation caused by nocturia may be particularly difficult for these younger patients because they are more likely to have active lifestyles and demanding work schedules.

There are no large differences in the prevalence of nocturia between men and women; however, voiding at least once nightly tended to be reported more frequently in younger

women than in younger men (20–44% and 11–35%, respectively), but is equally common or more so in men in older age groups [1], particularly after age 60 [5].

Interestingly, Tikkinen et al. reported that young women are more than 10 times more likely to have nocturia than young men in the Finnish population [20]. However, there are several studies reporting a similar rate of nocturia in men and women across all age groups [21, 22]. The reasons for the possible increased prevalence of nocturia in younger women versus men, and/or factors relating to study design which may lead to these varied findings, are subjects for further investigation. It may be that women experience greater fragmentation of sleep due to other causes (e.g., child care at night) or that they are simply more prone to insomnia than men and that these issues affect the reporting of nocturia. It is interesting to note that the studies that do indicate a gender difference in younger people come from several different countries and continents (Europe, Asia, Australia, and Canada). Therefore, the underlying reasons for this observation are unlikely to be confined to a specific country or culture [1].

Van Dijk et al. suggested that women start to develop nocturia at a younger age than do men, based upon their findings in a population-based survey designed to estimate the prevalence of nocturia in a representative sample of the adult population in the Netherlands [23].

In men, nocturia has been noted to be more significantly correlated with age than with bladder outlet obstructive symptomatology [24]. In another assessment of an elderly male population, 33% of 2,934 men had nocturia (greater than two episodes per night). However, multivariate analysis revealed the contributions of other pathologies to the symptom of nocturia including cerebrovascular disease, lower urinary tract (LUT) cancer, alcohol consumption, and treatment for voiding disorders [25].

The prevalence of nocturia, as with many other conditions, may be different among ethnic or cultural groups [19]. In fact, disparities in racial and ethnic presentations of nocturia have also been reported by several authors. Kupelian et al., in the BACH study, a large prospective assessment of a community-based population, identified an overall nocturia prevalence of 28.4% with higher prevalence rates in blacks (38.6%) and Hispanics (30.7%) as compared to white participants (23.2%) regardless of gender [26]. Similar findings have been observed by Sarma et al. in a study examining associations between diabetes and clinical markers of BPH in community-dwelling white and black men aged 40–79 years: black men had an increased association between irritative LUTS and diabetes [27]. However, Platz et al. reported that older black men were not more likely to have LUTS than were older white men with an apparent modestly higher prevalence of LUTS in older Mexican-American men [28]. Chuang and Kuo investigated the prevalence of LUTS, including nocturia, among indigenous and nonindigenous women in Eastern Taiwan and observed indigenous women have a higher prevalence of nocturia than nonindigenous women [29]. In a prospective comparison study, Mariappan et al. reported that nocturia, nocturia indices, and variables from frequency–volume charts are significantly different in Asian and Caucasian men with LUTS and they concluded that there are also possible ethnic differences in the causes of nocturia, with NP being more prevalent in Caucasians [30].

Table 2.1 Lower urinary tract factors associated with nocturia
Physiological change associated with aging (e.g., urogenital atrophy caused by estrogen deficiency)
Infravesical obstruction
<ul style="list-style-type: none">• Bladder outlet obstruction (BOO)• Urethral stenosis/urethral stricture
Nocturnal detrusor overactivity
<ul style="list-style-type: none">• Idiopathic (OAB)• Neurogenic (e.g., multiple sclerosis)
Detrusor hyperactivity with impaired contractility
Learned voiding dysfunction
Anxiety disorders
Pharmacological agents
Urinary stone disease (Ureteral calculi, bladder calculi)
Cystitis: bacterial, interstitial, tuberculosis, radiation
Cancer of the bladder, prostate, or urethra
Painful bladder syndrome/interstitial cystitis
Bladder hypersensitivity
Excessive nocturnal fluid input
Extrinsic compression (uterine fibroids, urogenital prolapse, ovarian tumor)
LUT surgery

Lower Urinary Tract Factors

Nocturia is the most prevalent of LUTS in the general community, as common in women as it is in men. Nocturia is also reported to be one of the most bothersome of LUTS, with greatest impact on the patient’s quality of life. Although the ICS report highlighted for the first time the unique nature of nocturia as a LUTS that can arise purely due to disorders outside the LUT, and recent researches have confirmed this phenomenon, it is clear that many LUT factors (Table 2.1) affect bladder function during both daytime and nighttime, such as age-related changes in LUT, BOO, OAB, and cystitis. Disorders such as reduced absolute bladder capacity due to radiation are unlikely to change. In contrast, functional disorders that affect storage capacity may indeed be altered as people lie down and/or enter different sleep stages. Little research has been done to explore the possible effects of position, sleep, and/or hypnotic medications on bladder function in health and disease [6].

Nocturia has been noted to occur in association with LUTS such as incontinence. Massolt et al. noted that 48% of incontinent women experienced nocturia which was due to either NP with or without changes in functional bladder capacity in 75% of 111 women undergoing assessment [31]. Klingler et al. identified the different factors contributing to nocturia in 324 patients in a multi-institutional study. Mean nocturia was 2.8 in men versus in 3.1 women. Fifty percent of patients were aged >65 years, 60% had daytime LUTS as well as nocturia. Principal causes for nocturia were global polyuria in 17%, NP in 33%, and reduced functional capacity <250 ml in 16.2%; 21.2% had mixed forms of NP and reduced bladder capacity and 12.6% suffered from other causes. Quality of life was significantly lower in women, in

patients aged >65 years and in those with reduced functional capacity. They concluded that nocturia had a high impact on bother score, strong associations with poor health, and other LUTS [7].

Age-related changes in the LUT may cause nocturia with or without other conditions such as NP or other LUTS. Detrusor contraction strength declines with age in women as well as men, and there is no DO-associated increase in contractility [5]. The alteration in collagen-to-smooth muscle ratio seen in later life leads to a “stiffer” bladder, with a lower elastic limit and may result in a reduction in functional bladder capacity and reduced sensation of bladder filling and thus LUTS, including nocturia [17].

Estrogen deficiency in postmenopausal women results in structural and physiologic changes, including urogenital atrophy, pelvic organ prolapse, pelvic floor relaxation, and neurogenic detrusor hyperactivity. Consequently, these alterations cause irritative symptoms and nocturia [18].

Age-related prostate epithelial hyperplasia is mediated by numerous stromal factors. It remains unclear whether prostatic inflammation (acute or chronic) contributes to urinary retention and LUTS in men [16].

Finally, both structural and functional changes occur with aging in the urinary tract and may increase the risk for development of nocturia, by decreasing bladder capacity and thus, nocturnal voided volume in both genders. In addition to the age-associated physiological changes to LUT function in later life, the elderly with nocturia appear to have a higher 24-h urine production than age-matched controls with no nocturia. These individuals also produce a higher proportion of their daily urine output at night [17]. Kawauchi et al. studied the role of reduced voided volumes in the elderly and analyzed nocturnal urinary frequency, time of voiding, and amount of each void in 188 healthy men (mean age 67.1 years) with no prostatic disease. Nocturnal urinary frequency increased with age from a mean of 0.61 voids per night at 55–59 years to 1.2 at 75–79 years. However, multiple regression analysis showed that nocturnal voided volumes and nocturnal urinary volume were independent determinants of nocturnal frequency; age was not an independent factor [32].

Diminished bladder capacity refers to a condition in which voiding occurs at bladder volumes less than functional bladder capacity, leading to awakening to void at night. Reduction in bladder capacity can occur at all times (reduced global bladder capacity) or exclusively at night (reduced nocturnal bladder capacity). Diminished global capacity is often related to urologic conditions, including BOO or decreased detrusor contractility resulting in increased postvoid residual urine volume (PVR), bladder irritation from stones, infection or neoplasm, extrinsic bladder compression from ovarian cancer or uterine fibroids, and decreased bladder capacity because of urogenital aging. BPH and OAB are two main urologic conditions associated with diminished bladder capacity [18] and just as there is a tendency to presume that nocturia in women is attributable to OAB, there is also a propensity for clinicians to attribute nocturia in men to prostatic problems, which can obstruct the bladder outlet and cause LUTS [6].

Among men with difficulty in emptying their bladder because of prostate enlargement, there is increased occurrence of LUTS, including nocturia. Nocturia and other

LUTS resulting from BOO are commonly associated with DO or high postvoid residuals. However, Chang et al. evaluated the cause of nocturia in a study of men and found that 83% had NP, 20% had NP alone, and 63% of patients had NP in combination with another factor such as small nocturnal bladder capacity, BOO, or sleep apnea [33]. Crucially, therefore, most male nocturia patients have NP, with or without comorbid prostatic problems. Men seeking help with their urinary problems are most frequently prescribed α 1-adrenoceptor antagonists and 5 α -reductase inhibitors or a combination of these. The impact of these drugs on relief of symptoms of BOO has been well demonstrated, but less information is available on how these treatments affect increased nocturnal frequency. A beneficial effect of terazosin and to a lesser extent, finasteride, has been shown. However, most of α 1 receptor antagonists interfere with blood pressure regulation and have a potential to cause postural hypotension. More selective α 1-AR antagonists have a reduced propensity to cause this adverse effect [17]. On the other hand, failure of traditional therapies for BOO often is attributable to the presence of underlying NP: Yoong et al. report that 85% of BPO patients with nocturia unresponsive to α 1-blocker treatment have NP [34]. Surgery (TURP) and traditional pharmacological therapies for BPO therefore frequently fail to provide a significant reduction in nighttime voiding [35, 36]. However, in the VA Cooperative Study Program Trial conducted by Johnson et al., 1,078 men with BPH having baseline nocturia of 2.5 episodes per night were randomized to receive empirical treatment with terazosin, finasteride, terazosin, and finasteride combined, or placebo. Nocturia episodes decreased to around two per night for all groups. No significant difference was found among any of the treatment arms, including placebo, suggesting that nocturia in men with BPH results from factors besides BOO [37].

Prevalence of the overactive bladder syndrome (OABS) increases in association with late life and is the a common cause of LUTS in the elderly. Nocturia commonly occurs as a result of this. Especially around menopause many women experience LUTS, including nocturia because of reduced endogenous estrogen production. Already existing symptoms often become worse when women enter menopause and if not treated, the condition further deteriorates [38]. When considering the symptom complex that constitutes the OABS, it is interesting to note that, in a European physician survey, nocturia was identified by only 5% of 355 physicians as the most important LUTS to resolve. However, 37% of those physicians identified it as the most difficult to deal with [17]. Weiss et al. studied 129 women ranging in age from 17 to 94 years. Of these 8% had NP, 62% had nocturnal DO, and 30% had a mixed form. Therefore, 32% must have had nocturia because of detrusor overactivity and no NP [39]. Brubaker and Fitzgerald report that, in the 62% of their OAB patients who had NP, solifenacin monotherapy led to no significant improvement in nocturia compared with placebo [40].

Increased urinary frequency may occur as a result of uninhibited detrusor contractions in neurological conditions such as a dementia, stroke, Parkinson's disease, and multiple sclerosis [19]. Urinary symptoms in patients with multiple sclerosis are usually secondary to spinal lesions, which interrupt neural pathways connecting the pontine micturition center to the sacral micturition center resulting

in DO, small bladder capacity, and nocturia [41]. Another interesting urodynamic observation particularly in elderly people is detrusor hyperactivity and impaired contractile function. It may present as urinary retention and thereby mimic prostatic outlet obstruction. Resnick et al. reported 33% of institutionalized incontinent elderly people to have this abnormality [42].

A range of urological and gynecological diseases such as UTI, BPH, radiation cystitis, interstitial cystitis, and cancer and estrogen deficiency may also increase nocturnal urinary frequency, usually by decreasing bladder capacity [19].

Medical (nonurological) causes of reduced voided volumes are exemplified by factors such as medications and anxiety disorders, and can usually be discerned from patient history [43].

Diuretics have been associated with a doubling in nocturia in both men and women; this may be partly because most patients take these oral medications in the morning [9]. In a study by Reynard et al., diuretics taken 6 h before going to bed resulted in substantially less nocturia [44]. In contrast to these results, a recent study by Rembratt et al. found no significant correlation between nocturia and diuretic use, when diuretics were presumably used for heart failure/hypertension [45]. The occurrence of ≥ 3 nocturnal voids was reportedly three times higher in women using analgesics daily than in those not using analgesics [9].

Cardiovascular

Nocturia can be caused by cardiovascular diseases, including congestive heart failure (CHF), coronary artery disease, hypertension, lower extremity venous stasis disease through third-spacing of fluid in the lower extremities, and cerebrovascular events such as stroke.

Several studies have also shown nocturia to be associated with cardiovascular disease. Klingler et al. identified the different factors contributing to nocturia in a multi-institutional study of 324 patients. Nocturia and its associated problems were evaluated using Kings' Health Questionnaires and voiding diaries in conjunction with concurrent health variables. Sixty percent of subjects had daytime LUTS as well as nocturia, one third had cardiac disease, 33% had cardiac pathologies, and 7% peripheral edema. NP was the most important contributor to nocturia [7]. In addition to several factors, the BACH study identified cardiac disease especially when associated with increased BMI as increasing the risk of nocturia [46]. In a case-control study with prevalence sampling, Tikkinen et al. explored the correlates for nocturia and their population-level impact in subjects (aged 18–79 years) from the Finnish Population Register. Although numerous correlates were identified, none affected $\geq 50\%$ of nocturia cases of both sexes. However, they found that coronary artery disease was associated with nocturia in the age-adjusted analyses for both sexes but for only women in multivariate analysis [4]. In the analysis by Coyne et al. of responses from 5,204 adults participating in the National Overactive Bladder Evaluation survey, a diagnosis of CHF was found as a risk factor for nocturia [21].

In a survey of adults at ages 60 years or greater, Johnson et al. found that hypertension was a significant predictor of nocturia more than once nightly [47]. Gourova et al. investigated the prevalence of nocturia and the predictive relationships with several factors, including cerebrovascular disease, cardiovascular disease, hypertension, and others in 2,934 elderly men. The prevalence of nocturia (two or more nocturnal voids) was 32.9%. They determined that nocturia in elderly men was significantly related to cerebrovascular disease. Also, BPH had a significant relationship with nocturia, especially in respondents with hypertension. Cardiovascular disease or hypertension was significantly related to nocturia, mutually replacing each other as a risk factor [25]. However, epidemiological researches of the association between nocturia and cardiovascular disease are not always in agreement and some studies have not found cardiovascular disease a correlate for nocturia [22, 48–50]. Finally, although the association between nocturia and cardiovascular diseases is clear, it may be crudely extrapolated that these conditions are relatively modestly increased in patients presenting with nocturia compared with levels in the background population. The majority of patients with nocturia in the related studies were not affected by these conditions. Therefore, the key causes of nocturia for most patients encountered in clinical practice are likely related to other factors [1] and this supports the conclusion that cardiac diseases are not the most common causes of NP in nocturics, particularly in the elderly [51].

CHF, especially in incompletely treated cases and right-sided disease, leads to NP as a result of an increase in the atrial natriuretic peptide (ANP) [52]. ANP is an important factor in controlling sodium excretion through its direct natriuretic effect, and suppression of renin and aldosterone secretion. With advanced age, the basal ANP level has been shown to be three to fivefold higher than those of young adults. Additionally, plasma rennin and aldosterone activities are also decreased with aging. Further, in patients with edema-forming states such as CHF or venous system dysfunction in the lower extremities, large quantities of fluid and solute accumulated in the lower extremities while standing during the day may become mobilized into the circulatory systems at night when the patient is supine [18, 51]. Torimoto et al. evaluated 34 men with NP using bioimpedance analysis, and identified correlations between nocturnal volumes and extracellular fluid and leg volume changes indicating a re-centralization phenomenon in at least some individuals with NP [53]. Consequently, atria are distended with the mobilized fluid in CHF and therefore, atrial pressure increases [50]. ANP is released by atrial myocytes in response to atrial distension and sympathetic stimulation. With the aforementioned hormonal changes, ANP affects the kidneys by increasing GFR and filtration fraction, which in turn produces natriuresis and diuresis [18] and nocturia is therefore common in persons with edema in the legs of various origin such as CHF and lower extremity venous dysfunction. On the other hand, circulating vasopressin can increase markedly in proportion to the severity of cardiac failure. NP in this disease cannot therefore be explained by impairment of the vasopressin system [51]. It was recommended that “considerable caution” be exercised in prescribing exogenous AVP (desmopressin or DDAVP) to patients with cardiovascular disease or hypertension, and DDAVP should not be used in frail elderly with nocturia because of the exaggerated risk of hyponatremia [5, 54].

Hypertension has previously been shown to be associated with NP and nocturia [55]. Hypertension might be related to nocturia by its effect on cardiovascular physiology (edema, CHF with atrial stretch, and release of ANP) or renal physiology (renal effects on glomerular filtration and tubular transport). Hypertension may cause resetting of the pressure natriuresis relation in the kidney [47]. Recently, Agarwal and colleagues have noted associations of nocturia with nondipping (failure to lower blood pressure during night and sleep) and effects on hypertension [56].

On the other hand, there is substantial evidence of an independent association between obstructive sleep apnea (OSA), nocturia, and cardiovascular disease, which is particularly in the case of hypertension and stroke (refer to Chapter 3) [57].

Short and fragmented sleep has been linked with an increased risk of cardiovascular disease, traumatic injury because of a combination of postural hypotension resulting in impaired balance and nocturnal awakenings for frequent visits to the toilet and urgency, and possibly mortality [14, 18]. Asplund reported that older people who voided three or more times at night had been reported to have a greater mortality over a 54-month period. Heart disease and autonomic dysfunction may be responsible for this increased risk [58]. Also, elderly people with disrupted sleep patterns have mortality rates due to cardiac disease, stroke, cancer, and suicide at least 1.5 times higher than those of elderly people who do not suffer from interrupted sleep [12].

Cardiovascular events are clustered in the morning hours, after increases in blood pressure and heart rate that accompany awakening and arising. Similar hemodynamic changes occur during the night after nocturnal awakening and getting up. Such changes are common among older patients who have nocturia frequently and rise to urinate. Burszty et al. tested the hypothesis that nocturia >2 times at night may be associated with increased mortality in a population sample of 456 subjects born from 1920 to 1921. Twelve-year survival was significantly lower among subjects reporting nocturia compared with those without nocturia. The interaction between nocturia and previous coronary heart disease (CHD) was highly significant. Survival of patients who had CHD with nocturia versus those without nocturia was 44% versus 66%. They concluded that nocturia is a significant independent predictor of mortality among 70-year-old patients with known CHD and thus warrants special attention [59].

Pulmonary

Patients with chronic obstructive pulmonary disease (COPD; bronchial asthma and pulmonary emphysema) have an increased airway resistance with related NP possibly due to increased renal sodium and water excretion mediated by raised concentrations of ANP [60]. Although the association between nocturia and lung disease has not yet been fully elucidated, the study conducted by Bing et al. is unique to show an independent association between nocturia and lung disease for the first time in a population-based study. They evaluated the association between

nocturia and several factors, including lung disease in a questionnaire study of 2,799 men and women and found lung disease was independently associated with nocturia and the association was strongly dependent on severity of nocturia, even though the study population diminished with advancing age. The authors postulated that the mechanism might be related to hemodynamic changes. Distension of the atria, acute hypoxia, and pulmonary hypertension has been reported to be responsible for an increase in ANP levels., leading to increased natriuresis and diuresis, which may play a role in the increase of nocturia episodes seen in these patients, though they stated that they did not know whether the similar mechanisms occur in patients with lung disease [50].

Also, Tikkinen et al. conducted a population-based study of 6,000 adults aged 18 to 79 years in Finland, studying nocturia and bother and health-related quality of life (HRQoL). They report that HRQoL worsens in proportion to an increase in the number of voids per night. In this study, nocturia was also associated with other comorbidities such as OSA and obstructive lung disease that also affect HRQoL [61]. Again, in a retrospective study, Oztura et al. demonstrated a significant association between nocturia and sleep disordered breathing, respiratory disturbance, sleep apnea–hypoxia, and low oxygen saturation [62]. However, Yosihimura et al. rejected an independent association between COPD and nocturia (≥ 2 voids) in their study [22].

Sleep-Related Factors (See Also Chap. 3)

Nocturia is a frequently described symptom that may be associated with a variety of sleep disorders [63], including insomnia, obstructive or central apnea syndrome, snoring, periodic or restless leg syndrome, parasomnias, sleep disorders related to medical disease, such as COPD, and sleep disorders related to neurological disease, such as Alzheimer's or Parkinson's disease and stroke [2] (Table 2.2). Sleep disturbance may be a cause or consequence of nocturia and these disorders causing nocturia may be related to concomitant medical or psychiatric conditions [64].

Sleep disorders are common particularly in the elderly and those are frequently the source of awakenings from sleep. The high incidence of both nocturia and sleep disorders in the elderly and other patients suggests that sleep disorders may be the cause of awakenings from sleep rather than nocturia [38]. Pressman et al. reported only 5% of his patients to correctly identify the source of their awakening from sleep. Most of awakenings from sleep attributed by the patients to be due to pressure to urinate were instead a result of sleep disorder [65].

The prevalence of nocturia in sleep disorders has not been extensively studied, even in OSA [63]. In an earlier study of women aged 40–64 years, Asplund and Aberg found that frequent nocturnal micturition was associated with poor sleep, daytime sleepiness, and impaired well-being [15]. In a home sleep study, the prevalence of OSA was double among urogynecology patients with nocturia compared with those without [66]. Klingler et al. reported that of NP patients with nocturia,

Table 2.2 Sleep-related factors leading to nocturia

Insomnia
Obstructive or central apnea syndrome
Snoring
Periodic limb movement disorders (periodic or restless leg syndrome)
Parasomnias
Sleep disorders related to medical disease (COPD, heart diseases, endocrine disorders such as thyrotoxicosis, acromegaly, rheumatoid arthritis, osteoarthritis, etc.)
Medications (corticosteroids, diuretics, β -adrenergic antagonists, calcium channel blockers, selective serotonin reuptake inhibitor antidepressants)
Sleep disorders related to psychiatric conditions (depression, anxiety, consumption and withdrawal of alcohol)
Sleep disorders related to neurological disease (Alzheimer’s disease, Parkinson’s disease, stroke, nocturnal epileptic seizures, dementia)

2.3% had sleep apnea [7]. Umlauf et al. reported nocturia to be closely associated with OSA in community dwelling older men and women [67]. Moriyama et al. found the prevalence of nocturia was high among patients with OSA and that OSA might have some relationship to nocturia without other voiding symptoms in men less than 50 years of age [68].

Nocturia has been reported to be an independent predictor of both self-reported insomnia and reduced sleep quality [69]. Yoshimura et al. investigated the differences and associations between bothersome (BN) and nonbothersome nocturia (NBN) and sleep disorders including insomnia, OSA restless leg syndrome (RLS), and periodic limb movement disorder (PLMD). Insomnia and OSA closely correlated with both NBN and BN, and PLMD correlated with BN. However, RLS was not associated with either NBN or BN [70].

Snoring has been associated with nocturia [71]. Oztura et al. reported that the prevalence of nocturia was 52% in individuals with primary snoring, 57.2% in individuals with mild OSA, 64.3% in individuals with moderate OSA, and 76.9% in individuals with severe OSA [62]. Gopal et al. reported that nocturia was associated with sleep disorders including OSA and insomnia in perimenopausal women [72]. Older African Americans have been reported to have twice the rates of sleep apnea of Caucasians, while a significant association between episodes of nocturia and symptoms of OSA was reported in African-American women [73, 74].

Nocturia is particularly bothersome for patients and their partners due to sleep disturbance [7]. The clinical implications of nocturia are naturally dependent on age and mobility, and on how often one has to get up during the night together with the ability to go back to sleep after returning to bed. Some have major sleep disturbances because of impaired sleep quality and daytime fatigue leading to lack of concentration [38].

However, deep, slow-wave, restorative sleep occurs during the first hours of the night, and lighter (less restorative) sleep predominates in the second part of the night. On the basis of the findings that it is mainly a decrease in deep sleep that contributes to daytime fatigue, researchers speculated that waking during deep sleep

would also be more likely to leave patients feeling groggy and tired the next day. Therefore, the quality of sleep and quality of life are affected not only by nighttime voiding frequency, but also by the timing of waking to void [75].

With increasing numbers of nocturnal voiding episodes, women are also more prone to experience poor appetite, unhappiness, and lack of confidence in the future. In addition, they paid more visits to doctors and received more medical treatment. The number of days on the sick list was five times higher in women with three or more voiding episodes than in those without nocturnal voiding [15].

OSA is manifested with symptoms of poor sleep quality, daytime sleepiness, snoring, and nocturnal leg movements. Nocturia is an independent predictor of severe OSA in patients with ischemic stroke. Severe OSA increases the risk of stroke recurrence and mortality after stroke [76]. Similarly, a recent retrospective study found that sleep-disordered breathing symptoms in poststroke subjects were associated with more episodes of nocturia [77].

The mechanisms for the association between OSA and nocturia severity might be multifactorial. NP is found in most nocturics and may be secondary to factors such as aging, stroke, and OSA [76].

Fluid Volume Disturbance

Fluid volume disturbance can be caused by several reasons and results in either global polyuria or NP as frequent causes of nocturia [2, 7, 60].

Global polyuria is defined as urine production in excess of 40 mL/kg of body weight over a 24-h period [2]. Physiologically, the rate of urine production is controlled by two factors: the concentration of urine and the rate of solute excretion. The former is determined by the antidiuretic hormone, arginine vasopressin (AVP), which acts upon connecting tubules and collecting ducts within the nephron via activation of V2 receptors to increase the amount of water reabsorbed from the glomerular filtrate. The latter is composed mostly of urea, sodium, and potassium whose rate of excretion is determined by diet and other factors influencing protein metabolism and the extracellular fluid volume [64]. Global polyuria has been linked to DM (type 1 and type 2) with associated osmotic diuresis; to the condition diabetes insipidus (DI) with its associated deficient production of antidiuretic hormone by the posterior pituitary (central DI) and resultant polydipsia and polyuria; and to conditions that impair the ability of the kidneys to respond to antidiuretic hormone (nephrogenic DI) (Table 2.3). Among these, the link between DI and global polyuria is the only association that is well supported by research, with documentation that treatment of DI results in resolution of polyuria [3]. In addition, global polyuria may be due to primary polydipsia (excessive fluid intake) which is distinguished from DI by water deprivation testing [18]. Patients with primary polydipsia can concentrate urine to 600–800 mOsm/kg whereas those with DI cannot. Patients with DI can be further substratified to central or nephrogenic via ability to concentrate urine caused by exogenously administered desmopressin, an ADH congener, in

Table 2.3 Causes of global polyuria

Osmotic diuresis
<ul style="list-style-type: none"> • Poorly controlled diabetes mellitus (Type 1 or Type 2) • Medications (e.g., mannitol, sorbitol)
Water diuresis
<ul style="list-style-type: none"> • Diabetes insipidus (DI) <ul style="list-style-type: none"> – Central (hypothalamic or pituitary lesions) – Renal (e.g., lithium, iatrogenic, hypercalcemia, hypokalemia, tetracyclines, hereditary, polyuric renal failure) – Gestational • Primary polydipsia <ul style="list-style-type: none"> – Psychogenic – Dipsogenic

patients with central DI. Primary polydipsia can be either psychogenic, characterized by aggressive water consumption due to psychological and cognitive impairment, or dipsogenic, caused by a primary abnormality in the thirst mechanism in the setting of a structural brain abnormality [64].

Nocturnal urine volume is defined as the total volume of urine passed during the night (including the first morning void). Healthy young adults between the age of 21 and 35 years old excrete $14 \pm 4\%$ of their total urine volume between 23:00 and 07:00 h whereas the more elderly people excrete $34 \pm 15\%$. Clearly, while many of the patients with polyuria may also have NP, there are other conditions which may present with nocturia. These may be summarized as those that cause a water diuresis alone and those that cause a combined solute and water diuresis [64]. NP is an overproduction of urine at night (defined as urinary output greater than 20% of the daily total in young individuals and greater than 33% in older individuals), which is offset by lowered daytime urine production resulting in normal 24-h urine volume [2, 43]. A state of altered hemodynamics is an important factor in the etiology of NP in patients with edema-forming states, such as CHF, hypoalbuminemia, nephrotic syndrome, venous insufficiency, and CKD. Enhanced ANP secretion because of medical conditions such as OSA can also cause NP. ANP is released by atrial myocytes in response to atrial distension and sympathetic stimulation. As stated previously, it affects the kidneys by increasing GFR and filtration fraction, which in turn produces natriuresis and diuresis. Theoretically, sleep deprivation can also change hemodynamics and thereby increase nighttime urine production, adding to the complexity of the relationship between sleep and nocturia. Moreover, there is some indication that nocturia can be resolved with treatment of OSA [1, 18]. The assertion by review articles that NP is linked to excessive evening fluid intake, evening caffeine intake, CHF with associated edema, autonomic dysfunction, kidney disorders, or central neurologic disorders is reasonable, but not supported by research that delineates the pathophysiology of these associations and/or the normalization of voiding patterns with treatment of the underlying problem. Without this supporting evidence, it remains a possibility that the clinical association is obscuring one or more other, perhaps more important contributors [3] (Table 2.4).

Table 2.4 Factors leading to nocturnal polyuria

Water diuresis
Abnormality in nocturnal secretion (or action) of AVP (nocturnal polyuria syndrome)
Primary – Idiopathic
Secondary – Behavioral factors (e.g., excessive fluid intake shortly before retiring, late-evening diuretic intake)
Solute/water diuresis
Edema-forming states (e.g., CHF, CKD, nephrotic syndrome, hypoalbuminemia, hepatic failure, chronic liver disease, venous insufficiency)
Comorbidities (e.g., autonomic nervous system dysfunction, Alzheimer’s disease, multisystem atrophy, stroke, Parkinsonism)
Sleep disordered breathing and sleep apnea syndrome
Renal failure
Estrogen deficiency

NP is often missed during the evaluation and diagnosis of nocturia despite the fact that it is perhaps the most common factor underlying nocturia [1]. Of men with LUTS suggestive of BPO, up to 95% may have NP [78]. Therefore, those patients will have no improvement even if they are given medical or surgical therapy for BOO.

Socioeconomic Factors

Socioeconomic factors have been associated with nocturia in a few recent reports, including marital status, education, employment, household income, and urbanization. However, the association is inconsistent among these studies. In the Boston Area Community Health (BACH) Survey conducted by Kupelian et al., the prevalence rates of nocturia by race/ethnicity and the contribution of socioeconomic status (SES) to potential differences by race/ethnicity were investigated in a random sample of 5,501 adults (2,301 men, 3,200 women) age 30–79. Nocturia was defined as voiding more than once per night in the past week or voiding more than once per night fairly often, usually, or almost always in the past month. Self-reported race/ethnicity was defined as black, Hispanic, or white. SES was defined as a combination of education and household income and categorized as low (lower 25% of the distribution of the SES index), middle (middle 50% of the distribution), and high (upper 25% of the distribution). They found that the effect of SES (education plus income) was more pronounced among men and among hispanic participants, while differences in prevalence of nocturia remained significant for black men and women. It was concluded that SES accounts for part of the race/ethnic disparities in prevalence of nocturia [26].

Burgio et al. studied the prevalence and correlates of nocturia (≥ 2 per night) in 1,000 community-dwelling older adults (aged 65–106) among whom African-American women, African-American men, white women, and white men were equally distributed. In-person interviews included social information (education, Mini-Mental State Examination, and rural versus urban dwelling). Nocturia was

more common in men than in women and more common in African Americans than whites. Higher Mini-Mental State Examination score was protective in men and a higher education was protective for women, while they did not report any effect of urbanization on nocturia [73]. However, Johnson et al. reported that restricting the sample to those with a high school education or greater made little substantive difference in the correlations between nocturia and the educational status in a population-based, community sample of noninstitutional adults aged 60 and older, initially collected in 1983 in the Medical, Epidemiologic, and Social aspects of Aging (MESA) Study [47].

In a study conducted by Hsieh et al., a total of 3,537 women aged 20–59 were interviewed face to face, assessing risk factors for nocturia among Taiwanese women aged 20–59 years. Marriage was found to increase the risk of nocturia in women [8].

Tikkinen et al. explored the correlates for nocturia and their population-level impact in a survey of 3,579 male and female subjects (aged 18–79 years) randomly identified from the Finnish Population Register (62.4% participated; 53.7% were female). Questionnaires also contained items on sociodemographic factors (marital status, education, employment, urbanization). They did not report a correlation between nocturia and any of these socioeconomic factors [4].

Female Reproductive/Gynecologic Factors

In women, LUTS including nocturia are often believed to result from aging, childbirth, menopause, or just “being a woman” [60, 79]. In fact, it is known that incontinence in women increases with the number of childbirths and the frequency of urogenital symptoms increases at ages around the menopause [15]. The LUT is known to be estrogen sensitive; reduced endogenous estrogen production at menopause may explain the increased incidence of urinary symptoms during menopause. Systemic estrogen replacement therapy appears to alleviate some of these symptoms [38].

Lack of estrogen contributes to ultrastructural changes of impaired contractility (e.g., detrusor fibrosis) in women, while low estrogen also may contribute to bladder muscle cell differentiation. In the urethra, closure pressure decreases by an estimated 15 cm H₂O per decade, possibly related to mucosal changes extending to the bladder trigone, irritating sensory afferent nerves, triggering DO, and both decreased urethral vascular density and blood flow. Circular smooth muscle mass and fiber counts decrease, with striated muscle loss in the anterior urethra. There is evidence for denervation in uterosacral ligaments and levator muscles, and decreased muscle fiber number, type, and diameter. Moreover, pelvic floor dysfunction, such as pelvic laxity has been postulated as a cause of nocturia, as well other LUTS [80]. Postmenopausal atrophy may cause loss of lactobacillus and colonization with pathogenic organisms (*E. coli*, enterococci), leading to higher rates of bacteriuria and symptomatic urinary tract infections [16] which contribute to nocturia as well as other LUTS.

Asplund and Aberg analyzed the relationship between nocturnal micturition and gynecological factors such as parity, menstrual status, menopausal symptoms, and hormone replacement therapy in 3,669 Swedish women aged 40–64 years. Of women with no nocturnal micturition, 13% were receiving HRT, whereas the corresponding proportions in women treated HRT having one, two, and three or more nocturnal voiding episodes were 21, 23, and 28%, respectively. The number of nocturnal voiding episodes was unaffected by parity. The absence of an increase in nocturia in women of this study after several childbirths may support the view that nocturia can also be caused by other factors than disturbances in the distal urinary tract [15].

Tikkinen et al. evaluated the association of nocturia and urinary urgency with reproductive factors, including parity, the postpartum period, menopause, hormone replacement therapy, hysterectomy, and surgery for stress urinary incontinence (SUI) in randomly selected 2,002 women aged 18–79 years. Parity, postpartum (defined as 6 weeks to 1 year after delivery) and postmenopausal periods were associated with increased nocturia, but hormone therapy and hysterectomy were not. These authors found nocturia to be associated with parity when assessed independently of menopausal status [81].

Hsieh et al. analyzed the relationship between nocturia and some gynecological factors in 3,537 Taiwanese women aged 20–59 years and found that there was no relationship between nocturia and parity, menopause or hormone therapy. Although the women who underwent hysterectomies had a higher rate of nocturia than those who did not, the difference was not statistically significant [8]. Bing et al. reported no association between nocturia and parity, hysterectomy, pelvic organ prolapse, or urinary incontinence surgeries [50]. Similarly, Burgio et al. found history of HRT and hysterectomy to be unassociated with nocturia [73].

Lifestyle and Behavioral Factors

Many epidemiological studies have implicated lifestyle and behavioral factors to increase the risk for nocturia. These factors include body mass index (BMI) and obesity, fluid intake particularly at night, smoking and physical activity. Shiri et al. investigated the effects of lifestyle factors such as obesity, smoking, alcohol and coffee consumption on the incidence of nocturia in a sample of 1,580 men and found obesity to increase the risk of nocturia. The link between other lifestyle factors and nocturia is weak for alcohol consumption and absent for both smoking and coffee consumption [82].

There are potentially modifiable risk factors for nocturia in adults. Recently, Soda et al. conducted a prospective evaluation of 56 patients treated at three hospitals between 2005 and 2009 for symptomatic nocturia to test the efficacy of nondrug lifestyle measures as a first step in treating nocturia and found factors predictive of the efficacy of the intervention. Lifestyle modifications consisted of four directives of (1) restriction of fluid intake, (2) refraining from excess hours in bed, (3) moderate

daily exercise, and (4) keeping warm in bed. The frequency volume chart, International Prostate Symptom Score, and Pittsburgh Sleep Quality Index before and 4 weeks after the intervention were used to evaluate the efficacy of therapy. The authors reported that mean nocturnal voids and nocturnal urine volume decreased significantly from 3.6 to 2.7 and from 923 to 768 ml, respectively. Fifty-three percent improved by more than one episode. They concluded nondrug lifestyle measures to be effective in decreasing the number of nocturia episodes and to improve quality of life. Patients with polyuria had a better response to this regime [83].

On the other hand, Nakagawa et al. reported a significantly increased mortality risk for nocturics (≥ 2 voids per night) compared with those people who experienced < 2 voids per night. This risk was independent of many possible contributing comorbidities or lifestyle factors such as BMI, smoking and alcohol consumption, possibly due to fragmentation of sleep itself, and the health consequences of poor sleep [84, 85].

BMI and Obesity

Several epidemiological studies have consistently reported higher BMI or obesity as an important risk factor for nocturia, although the exact mechanism by which obesity causes nocturia is not known [86]. However, it confers increased risk for sleep apnea that is frequently associated with nocturia [43].

Tikkinen et al. analyzed the association of nocturia with overweight and obesity in over 3,500 randomly selected Finns aged 18–79 years. Self-reported body weight and height were used to calculate BMI. Subjects were classified on the basis of BMI as nonoverweight (BMI < 25), overweight (BMI 25–29.9 kgm²), or obese (BMI ≥ 30). Among men, the age-standardized prevalence of nocturia, defined as at least one void per night, was 33.4% in the nonoverweight, 35.8% in the overweight, and 48.2 in the obese. Among women, the corresponding figures were 37.2% in the nonoverweight, 48.3% in the overweight, and 53.6% in the obese. The authors conclude that obesity is associated with increased nocturia, more strongly among women than among men [87]. The same author and colleagues supported their initial findings stated earlier in a follow-up study. Nocturia was correlated with obesity for both sexes and with overweight for women [4]. Similar findings were reported in several other studies [8, 50, 73, 82].

Asplund assessed the relationship of nocturia to body weight in a questionnaire survey among 6,103 men and women with a mean age 73 and 72.6 years, respectively. BMI was 25.4 in men and 25.4 in women. BMI/obesity increased in parallel with increased nocturnal voiding, and both nocturnal eating and daytime loss of appetite increased correspondingly. The pattern of increase of these symptoms might support the interpretation that frequent nocturnal micturition increases the risk of obesity, partly as a consequence of its negative impact on sleep [88]. The findings of two reports from the BACH Survey showed that nocturia-related increase in prevalence with increasing BMI is in agreement with other studies [26, 46].

Interestingly, Laven and colleagues found that low subject low birth weight and abdominal adiposity (waist-to-hip ratio) are associated with increased risk of moderate to severe LUTS, including nocturia in adults [89].

Fluid Intake

Despite controversial findings, there is fair evidence of a relation between nocturia and fluid intake, particularly consumption of excess amount of fluid at evening including water, beverages, alcohol, coffee, and tea as a dietary habit. They can result in increased urinary volume, especially at night and may initiate NP that is the main cause of nocturia.

Klingler et al. found that, of 150 nocturic patients due to NP, 25.4% had high evening fluid consumption (more so in men than in women). Women had a significantly higher mean 24-h urine output than men and more women than men had a voided urine volume >2,400 ml. It is unclear whether these findings are related to different drinking habits; perhaps women tend to drink higher fluid volumes throughout the entire day, as part of what may be perceived to be a healthy lifestyle habit [7]. Mono-symptomatic polyuria >2,800 ml due to excessive fluid intake was an unexpectedly common cause nocturia in that study: in 17% of patients this was the sole etiology for nocturia. In contrast, Johnson et al. reported that nighttime fluid and coffee intake were not associated with nocturia in a sample of community-living older adults [47].

Many older people also adopt rigid drinking habits, which include fluid intake late into the night, frequently including alcohol [17]. These habits are usually associated with high nocturnal urine production and resulting nocturia [19] (Fonda 1999).

Yoshimura et al. showed that alcohol consumption impacts the prevalence of nocturia. Interestingly, moderate alcohol consumption had been reported to prevent nocturnal voiding; men drinking three times a week had a lower risk of nocturia than those drinking alcohol more, or less, often [25]. However, coffee or alcohol consumption has been shown in several recent studies not to be associated with nocturia [4, 8, 26, 47, 50, 73].

AVP is responsible for regulating urine production with a diurnal pattern in healthy people. The rhythm appears to be linked to the wake-sleep cycle rather than to the time of day. With advancing age, nocturnal secretion of AVP becomes blunted, resulting in similar day- and nighttime blood levels of AVP and hence to an increase in nighttime urine production. Also, renal concentrating capacity is reduced with age due to impaired renal tubular response to AVP. The ability of the kidney to retain sodium also decreases with advancing age: after administration of an acute water load, there is exaggerated natriuresis in older people compared with younger individuals [12].

Other hormones likely to play a role in altered renal sodium handling of elderly people are the renin-angiotensin-aldosterone system and ANP. The renin-angiotensin-aldosterone system is modulated by ANP, with high levels of ANP

reducing renin secretion and leading to a decrease in plasma aldosterone [90]. It is evident that an increase in nighttime urine excretion, causing individuals to rise and void, is part of the normal aging process. Healthy people aged 62–70 years who consume a normal amount of dietary sodium have lower levels of both active plasma renin and aldosterone in the supine position than healthy individuals aged 20–30 years. The reduction in the formation of active renin in older individuals may, in part, be responsible for the decreases in the plasma concentrations of active renin and aldosterone and accompanying natriuresis during sleep-related recumbency [12].

On the other hand, the type of fluid intake appears to be important. A vasopressin-insensitive state may be caused by ethanol, resulting in a polyuric state. Caffeine-rich fluids like coffee and cola have been reported to increase smooth muscle contractility, which may aggravate existing detrusor instability and worsen frequency and nocturia [91, 38].

Smoking

The findings from several studies on relationships between nocturia and smoking are inconsistent. Asplund and Aberg reported that nocturnal micturition episodes were increased by smoking in women [92]. By contrast, Bing et al. reported that current smokers were significantly less likely to have nocturia of ≥ 1 voids than nonsmokers; smoking was inversely associated with nocturia in a Danish population of men and women aged 60–80 years [50]. The latter findings support results reported by Yoshimura et al. [22]. This apparent protective effect of smoking can be explained by the effect of nicotine increasing arginine vasopressin secretion that decreases nocturnal urine volume [93]. Moreover, clinical studies suggest that smoking and/or nicotine intake decreases nocturnal urine production [47, 50]. On the other hand, Tikkinen et al. reported smoking not to be associated with nocturia in the FINNO study [4]. Again, there was no relationship between nocturia and smoking in two further studies [8, 82].

Physical Activity

Until the BACH Survey [26], we had no information on a possible relationship between physical activity and nocturia, because this relationship was rejected in a prior study conducted by Schatzl and co-workers [94]. The BACH Survey demonstrated that increased physical activity was associated with decreased odds of nocturia [26]. Recently, Agarwal et al. reported that increased nighttime physical activity contributed to nondipping blood pressure patterns in chronic kidney disease (CKD) patients, possibly exacerbating nocturia [56]. However, the association between nondipping and nocturia remains unclear [18]. Interestingly, a questionnaire-based study analyzing

the relationship of nocturnal micturition to regular exercise as well other factors in 3,669 women from Sweden reported lack of regular exercise to be associated with an increased number of nocturnal micturition episodes [92].

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(Eds.)

2012, XII, 172 p., Hardcover

ISBN: 978-1-4614-1155-0